IN THE UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF TEXAS
(HOUSTON DIVISION)

GAYATHRI MURTHY, Plaintiff,	§ § §	
v.	§	CASE #: 4:11-cv-00105-KPE
ABBOTT LABORATORIES, Defendant.	§ § §	

PLAINTIFF'S RESPONSE IN OPPOSITION TO DEFENDANT'S MOTION FOR SUMMARY JUDGMENT ON CAUSATION

Respectfully submitted,

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At first blush, one wonders why Abbott's counsel devoted 25 pages to a separate Motion for Summary Judgment based on an asserted lack of causation evidence when they had already filed an extensive Memorandum seeking to exclude Plaintiff's causation experts' testimony under *Daubert* and its progeny. Much of the material is duplicative. On closer examination, however, it become apparent that, *in addition* to seeking a "win" under federal procedural/evidentiary standards, Abbott also raises a briefly intriguing substantive argument under Texas law. It necessitates a response.

Prior to giving that response, however, it is imperative that we recap the arguments supporting the admissibility of the expert opinion testimony, and other evidence of general causation, and that we specifically **incorporate by reference** the lengthy reply to that motion as well as all other related briefing being filed this date. In a nutshell, the general causation *Daubert* motion is trumped, as a matter of law, by the following recent in-court testimony of Abbott's own witness, Dr. David Feigal:

> *Q.* *Okay. So if they're in the warnings, there's reasonable evidence of a causal association, true?*
>
> *A.* *Yes, that's the standard.*
>
> * * *
>
> *Q.* *Lymphoma?*
>
> *A.* *Yes.*

The testimony was focused on the legal, regulatory and scientific significance of the warning information contained in the current label.

Under the 2006 amendments to the FDA labeling regulation, 21 CFR §201.57, Abbott could not have put these words in its Humira label unless Abbott itself believed that there is "reasonable [scientific] evidence" of a "causal association." Moreover, in one of the key cases cited by Abbott,

Perry v. Novartis Pharmaceuticals Corp., 564 F. Supp. 2d 452, 468 (E.D. Pa. 2008), the court writes that "**lymphoma caused by immunosuppressant drugs is well-understood.**" Indeed, it now is.

The FDA Guidance for Industry concerning §201.57 articulates the various scientific data points and considerations that should be considered as evidence of this "causal association." They are remarkably similar to the "Bradford Hill" factors that courts assess in determining whether an expert's opinion on general causation is sufficient to pass *Daubert* muster. *Compare* FDA GUIDANCE FOR INDUSTRY: **Warnings and Precautions . . . Content and Format** (October 2011)[1] *with* REFERENCE MANUAL ON SCIENTIFIC EVIDENCE: Third Edition, Reference Guide on Epidemiology, Section V at pp. 375-76 (National Academies Press, 2011). Notably, nowhere in either of these two authorities is evidence of causation strictly limited to epidemiologic data.

Abbott's lawyers beat the drum quite loudly about favorable epidemiology. But it is a much different story altogether in the confines of Abbott's internal risk management discussions. In its confidential, 2011 Risk Management Plan Abbott, Abbot makes a critical distinction that is dispositive on causation:

> **Important AEs [adverse events] with adequate evidence of an association with adalimumab treatment were categorized as important identified risks**. Important AEs for which there is some basis for suspicion of an association with adalimumab or other TNF -antagonists treatment, but where association has not been confirmed, were categorized as important potential risks.

Exhibit B at 26 (Risk Management Plan)(FILED UNDER SEAL)["FUS"](emphasis added)[2]. Based on Abbott's briefing in this case one would have to assume that Abbott would catagorize lymphoma as a "important potential risk" as stated above. But that is not the case. Abbott categories lymphoma

[1] Exhibit A, hereto at 3 discussing what is, for all intent and purposes, the Bradford-Hill factors.

[2] This Risk Management Plan is 550 pages long. For the sake of brevity only the first and applicable pages are provided to the Court. Should the Court desire the entire document, counsel will readily provide it.

as "**an important identified risk.**" *Id*. at 54. This designation can only made when there is "adequate evidence of an association" between lymphoma and Humira. *Id*. at 26. This document alone is enough to deny Abbott summary judgment on causation and *Daubert*.

The head of Abbott's Pharmacovigilance (Dr. James Embrescia) also believes that epidemiology is but one factor used in assessing whether or not a drug is related to an adverse event:

> Q: So you'd agree that when trying to make an assessment to the relationship between an individual person, the drug, and the adverse event, epidemiology would be one factor to consider in making that determination but not the only factor?
>
> A. That would be true.

Exhibit C at 32:5-32:11 (Deposition Excerpts of Dr. James Embrescia)[FUS]. All told, the record before the Court illustrates how epidemiology is not the be all, end all, when it comes to medical causation.

Summary of the Argument

Contrary to Abbott's arguments, the Fifth Circuit has not yet resolved the intriguing jurisprudential debate about whether the *Havner-Garza* 2.0+ standard controls in a federal diversity trial. Interestingly, the most on point word from the Fifth Circuit suggests that Texas courts apply federal *Daubert* standards–not that federal courts should apply Texas *Havner* standards.

In any event, this dispute is probably not outcome determinative for two very important reasons. First, the plaintiff does not rely solely on epidemiological evidence. Abbott has judicially admitted that there is "reasonable scientific evidence of a causal association" between Humira and lymphoma, and, indeed, has even identified the "biologically plausible" mechanism in its label. This, plus the admissible testimony of Dr. Gershwin, using the "Bradford Hill" standards, establishes general causation. The report and deposition of oncologist, Dr. Dean McCracken, reflects that, with regard to his specific causation opinion, he used a time honored "differential diagnosis" and that he

did consider and weigh all of the potential alternative causes of Gayathri Murthy's lymphoma, (including "idiopathic") before concluding that one of the most probable legal causes, or "substantial factors," was her exposure to Humira. This defeats summary judgment.

Second, while there admittedly is epidemiological evidence to support Abbott's statistical significance mantra– some of it sponsored, or even "ghost-written" by Abbott – there **are** more than two published epidemiological studies that have statistically significant relative risks of 2.0+ between TNF alpha blockers like Humira and malignancies. Thus, even the draconian standards of *Havner-Garza* are satisfied by the record in this case.

Argument and Authorities

I. FEDERAL RULES OF EVIDENCE GOVERN THIS FEDERAL TRIAL.

Abbott insisted on having this case in a federal forum. This case was initially filed by other counsel for the plaintiff in federal district court in Massachusetts. One of the conditions that Abbott imposed in the Tolling Agreement for the stipulated dismissal of that case without prejudice was that it had to be refiled within a certain period of time and "in the United States District Court for the Northern District of Illinois or United States District Court for the Southern District of Texas." Exhibit D at 1 (Tolling Agreement of 10/20/10, referenced in Doc. 39, Memorandum and Order (November 8, 2011)).

There is an obvious tactical reason for Abbott's choice of a federal forum. As a general rule, Abbott prefers federal *Daubert* jurisprudence to the rules of evidence in the state courts of its home state of Illinois, where the vast majority of the Humira injury cases are pending. The reason is clear. Illinois Rule of Evidence 702 specifically rejects *Daubert* in favor of *Frye*, but only applies that standard with regard to "novel" theories of science or medicine. Having insisted on this federal forum, however, Abbott cannot have its cake and eat it too.

A. Comity's 1938 Flip-Flop. Prior to 1938, federal courts applied *federal* common law, even in diversity jurisdiction cases, but, generally speaking, applied state court rules of procedure and evidence. The 1938 decision in *Erie RR v. Tompkins*, changed the former; the 1938 promulgation of the Federal Rules of Civil Procedure the latter.

Any remaining question as to whether federal courts sitting in diversity applied federal or state rules of evidence were resolved by the 1972 promulgation of the Federal Rules of Evidence. For the next several decades, there were advantages to be won, or lost, based on the choice of a federal or state venue. For example, for a period of time, Rule 407's exclusion of post-remedial measures did not apply to strict tort liability cases under the specific wording of the Texas analog to that rule.

Nevertheless, under the *Erie*/FRCP paradigm, there is no question but that Texas substantive law governs this Texas diversity case.[3] Nor should there by any debate about the fact that federal procedural/evidentiary standards govern those aspects of the case.

B. The Relative Risk of 2.0+ Imbroglio. An argument has been made by some popular writers concerning the intersection of law and science that a relative risk of 2.0+ in scientific jargon equates to the "preponderance of the evidence" in legal speak.

There was a time, shortly after *Daubert* itself was decided, when it appeared that federal courts might adopt the bright line rule of 2.0. Judge Kozinki's lamentation on remand of *Daubert* itself is an excellent example. In that case, which is the scientific opposite of this one, the experts

[3] Abbott does overplay its hand a bit by saying that "This Court has previously held that Texas law governs this diversity jurisdiction case," Doc. 139 at p. 15/32, citing this Court's now withdrawn opinion at *Murthy v. Abbott Laboratories,* 847 F. Supp. 2d 958, 967 (S.D. Tex. 2012), reconsideration denied (May 2, 2012). What the Court said was, in the absence of some question about it being raised by the plaintiff, it would apply Texas substantive law. *Id*. at n.4.

did not know *how* Bendectin could cause birth defects, but honestly believed that it really did. Judge Kozinski explained that:

> Not knowing the mechanism whereby a particular agent causes a particular effect is not always fatal to a plaintiff's claim. Causation can be proved even when we don't know precisely how the damage occurred, if there is sufficiently compelling proof that the agent must have caused the damage somehow. One method of proving causation in these circumstances is to use statistical evidence.

Daubert v. Merrell Dow Pharmaceuticals, Inc., 43 F.3d 1311, 1314 (9th Cir. 1995)[hereinafter *Daubert II*](emphasis added). The very clear implication of that opinion, however, was that IF an expert could provide a biologically plausible explanation to provide the "how," then the case would be submitted to a jury. Dr. Gershwin has provided the "how." Indeed, the Humira label itself shows us the "how," *i.e.,* via immunosuppression. In full accord with Dr. Gershwin, Abbott's own case, *Perry*, holds that "lymphoma caused by immunosuppressant drugs is well-understood." *Perry v. Novartis Pharmaceuticals Corp.*, 564 F. Supp. 2d 452, 468 (E.D. Pa. 2008).

Judge Kazinski's *Daubert II* opinion is labeled as a "lamentation," in part, because of the following very candid words of caution:

> Our responsibility, then, unless we badly misread the Supreme Court's opinion, is to resolve disputes among respected, well-credentialed scientists about matters squarely within their expertise, in areas where there is no scientific consensus as to what is and what is not "good science," and occasionally to reject such expert testimony because it was not "derived by the scientific method." Mindful of our position in the hierarchy of the federal judiciary, we take a deep breath and proceed with this heady task.

Id. at 1316. With breath held, the Court decided to chart these unsettled waters by adopting a "bright line" standard. In those cases where – because of the absence of a biologically plausible mechanism or other "Bradford Hill" type indicia of scientific proof – a plaintiff had to rely *solely* on statistical

evidence from epidemiological studies, only statistically significant relative risks (or other barometers of risk) in excess of 2.0 would do the trick. *Id*. at 1320-21.[4]

In the 20 years since *Daubert II* was handed down, the majority of federal circuits have rejected the 2.0 rule. *See e.g., In re Neurontin Mktg., Sales Practices, & Products Liab. Litig.*, 612 F. Supp. 2d 116, 132 (D. Mass. 2009). So, too, does Abbott's epidemiology expert, Dr. Ory. *See* Section III.B., *infra* and Dr. Embrescia's testimony, *supra*. Unfortunately, the Fifth Circuit has not squarely addressed it. Nevertheless, without question, in Texas state courts those plaintiffs who must rely on epidemiological evidence to prove their cases must do so under the RR = 2.0+ standards of *Havner-Garcia*.

C. The Fifth Circuit Has Not Yet Decided Whether the *Havner* Rule of 2.0 Is Substantive or Procedural. A footnote in a 1998 panel opinion raised the issue:

> *Havner* amounts to the Texas Supreme Court's definition of "more likely than not burden of proof." *See Havner*, 953 S.W.2d at 717. **Arguably, the definition of the applicable burden of proof is procedural rather than substantive, and therefore controlled by federal rather than state law.** *See Gasperini v. Center for Humanities, Inc.*, 518 U.S. 415, 426, 116 S.Ct. 2211, 135 L.Ed.2d 659 (1996)(noting that classification of a law as "substantive" or "procedural" is "sometimes a challenging endeavor.") The Fifth Circuit has not weighed in on the question of whether evidence must show more than doubling of the risk to support a jury's finding of causation.

Bartley v. Euclid, Inc., 158 F.3d 261, 273 (5th Cir. 1998)(emphasis added) reh'g en banc granted, opinion vacated, 169 F.3d 215 (5th Cir. 1999) and on reh'g en banc, 180 F.3d 175 (5th Cir. 1999). However, as the citation reflects, this panel opinion was vacated. The en banc court affirmed the plaintiff's verdict and judgment, and the trial judge's decision to admit expert testimony on the basis

[4] Even this ruling, however, was not quite as "bright line" as a Big Pharma lawyer might like. Footnote 16 of the court's opinion left a little wiggle room: "A statistical study showing a relative risk of less than two could be combined with other evidence to show it is more likely than not that the accused cause is responsible for a particular plaintiff's injury." *Id.*

of *Daubert* and *Joiner*, and with no citation to *Havner* whatsoever. *Bartley v. Euclid, Inc.*, 180 F.3d 175, 179 (5th Cir. 1999).

Abbott's principal citation in support of the notion that Havner establishes a substantive rule *that governs diversity cases is the Western District's opinion in Cano v. Everest Minerals Corp.,* 362 F. Supp. 2d 814, 821-22 (W.D. Tex. 2005). Judge Rodriguez's opinion there very clearly adopts *Havner* standards as setting forth what is *legally sufficient* or required by Texas substantive law in a diversity case. Because the case was not appealed, there is no Fifth Circuit review. In *Lofton v. McNeil Consumer & Specialty Pharmaceuticals,* 682 F. Supp. 2d 662, 669 (N.D. Tex. 2010) aff'd, 672 F.3d 372 (5th Cir. 2012), however, Judge Lindsay of the Northern District declined to follow *Cano* with regard to a *Daubert* challenge, but stated that he would follow *Havner* with regard to the legal sufficiency of the evidence in a summary judgment context. Confusing precedent at best. The well known Fifth Circuit opinion in that case has nothing to do with either the admissibility or sufficiency of expert testimony of causation.

The two Fifth Circuit cases that *Cano* cites in support of its holding that *Havner* is substantive rather than procedural are *Wells v. SmithKline Beecham Corp.*, 601 F.3d 375, 380 (5th Cir. 2010) and *Knight v. Kirby Inland Marine Inc.*, 482 F.3d 347, 354 (5th Cir. 2007)(citations omitted). Neither holds that *Havner* is substantive, and neither holds that epidemiological evidence is *sine qua non*. In fact, both make rather common sense notions about the significance of this evidence. The *Knight* court candidly acknowledges that "in epidemiology hardly any study is ever conclusive, and we do not suggest that an expert must back his or her opinion with published studies that unequivocally support his or her conclusions." *Id.* at 354. Although it cites *Havner* for the unremarkable proposition that a party in a drug or toxic tort case must prove general causation, it is

clear from the extensive citations to *Daubert* and its progeny that the Fifth Circuit judged the admissibility *vel non* of the experts' testimony under federal, not Texas, evidentiary standards.

Wells, which cites *Knight* extensively, gets Abbott a bit closer, . . . but not there. Here is the Court's conclusion:

> Our conclusion that the trial court did not abuse its discretion is an unremarkable sustaining of the district court's gatekeeping role under *Daubert*. In finding the evidence scientifically unreliable-and thus insufficient to prove causation under Texas law-it follows that the experts' testimony was also deficient under *Daubert* given its overlap with Texas questions of scientific sufficiency.[32]

Wells v. SmithKline Beecham Corp., 601 F.3d 375, 381 (5th Cir. 2010). The text of footnote 32 reflects the Fifth Circuit's understanding that Texas has embraced *Daubert* standards for review of the legal sufficiency of evidence in "no evidence" motions for directed verdict or JNOV, **not vice versa:**

> The Supreme Court of Texas has explained that "the same factors may be applied" to "no evidence review of scientific evidence" as to review of admissibility of scientific testimony. *Merrell Dow Pharms., Inc. v. Havner,* 953 S.W.2d 706, 714 (Tex.1997) (referencing *E.I. du Pont de Nemours & Co. v. Robinson*, 923 S.W.2d 549, 556-57 (Tex.1995) (adopting the federal *Daubert* standard in the Texas-law inquiry into the admissibility of expert testimony)); *id*. at 712 (explaining that scientific sufficiency in Texas "is determined by looking at numerous factors including those set forth in ... *Daubert*").

Id.

Thus, the clearest indication from the Fifth Circuit is that federal courts will apply federal evidentiary standards to the admissibility vel non of proof, and, of course, federal procedural standards to motions for summary judgment, directed verdict, and judgment as a matter of law. Frankly, it is what comity and federalism require.

II. NEITHER *HAVNER* NOR *GARZA* REQUIRE ONLY EPI EVIDENCE.

Assuming, *arguendo*, that *Havner* and its progeny establish substantive rules of law that will govern the outcome of this case, we start with a very careful parsing of what the case held, and what it did not. In two key paragraphs, the *Havner* court made clear that it was not tossing all of the other scientific factors out of the window by its holding, but that with regard to epidemiological studies only, a doubling of the relative risk was required:

> We do not hold, however, that a relative risk of more than 2.0 is a litmus test or that a single epidemiological test is legally sufficient evidence of causation. Other factors must be considered. . . . Likewise, even if a particular study reports a low relative risk, there may in fact be a causal relationship. The strong consensus among epidemiologists is that conclusions about causation should not be drawn, if at all, until a number of criteria have been considered. One set of criteria widely used by epidemiologists was published by Sir Austin Bradford Hill in 1965. Another set of criteria used by epidemiologists in studying disease is the Henle–Koch–Evans Postulates. Although epidemiologists do not consider it necessary that all these criteria be met before drawing inferences about causation, they are part of sound methodology generally accepted by the current scientific community.
>
> * * *
>
> A few courts that have embraced the more-than-double-the-risk standard have indicated in dicta that in some instances, epidemiological studies with relative risks of less than 2.0 might suffice if there were other evidence of causation. *See, e.g., Daubert*, 43 F.3d at 1321 n. 16; *Hall*, 947 F.Supp. at 1398, 1404. We need not decide in this case whether epidemiological evidence with a relative risk less than 2.0, coupled with other credible and reliable evidence, may be legally sufficient to support causation. We emphasize, however, that evidence of causation from whatever source must be scientifically reliable.

Merrell Dow Pharmaceuticals, Inc. v. Havner, 953 S.W.2d 706, 718-19 (Tex. 1997).

Numerous decisions citing *Havner* have been decided in the sixteen years since it was handed down.[5] The most important under Texas law is the Supreme Court's 2011 decision in *Merck & Co., Inc. v. Garza,* 347 S.W.3d 256, 262 (Tex. 2011). It reviewed and reaffirmed the *Havner* decision. Under *Garza*, IF a plaintiff must rely on epidemiological evidence, there must be two studies that show a doubling of the risk. However, even under this opinion, there are caveats and limitations. First, the Supreme Court acknowledged that "[c]ausation can sometimes be proved directly" but that "[o]ften, however, it can be proved only indirectly, with epidemiological studies." *Id*. at 263. Therefore, once again, it did not hold that epidemiological studies are *sine qua non*. To the contrary, it leaves very clear room for a holding on this record that, given the admissions by Abbott in its labeling and by its experts, and given the clear explication by Drs. Gershwin and McCracken of the role of immunosuppression in causing lymphoma, there is ample proof for this case to go to a jury.

Second, it echoed the *Havner* holding that "[c]ourts should allow a party, plaintiff or defendant, **to present the best available evidence,** assuming it passes muster under *Robinson." Id*. at 266 (emphasis added). Third, it reaffirmed the *Havner* holding that reliable scientific evidence, whether epidemiological or otherwise, should be judged via the Bradford Hill factors. *Id*. at FN 41.

But with respect to this case, and as more fully discussed in Plaintiff's *Daubert* brief, the evidence of general causation in this case goes so far beyond epidemiology as to make this inquiry almost irrelevant. Abbott admits biological plausability, reasonable association, statistically significant clinical trial data showing increased rates and risk, "probable" causality assessments by clinical investigators, and internal discussions acknowledging true causal relationships between Humira and malignancy in specific patients. None of this even touches on the overwhelming

[5] An intermediate appellate opinion handed down in 2011, the same year as *Garza*, demonstrates how Texas state courts are still looking to the *Robinson* factors and to the Bradford Hill criteria, to assess scientific reliability of expert testimony. *Faust v. BNSF Ry. Co.,* 337 S.W.3d 325, 337 & nn. 20-21 thereto (Tex. App. 2011), review denied (July 1, 2011), reh'g overruled (Mar. 10, 2011).

Bradford-Hill evidence that Dr. Gershwin chronicles or the FDA's "reasonable scientific evidence" standard for label inclusion. Nevertheless, as the Court will see in the upcoming section, there is enough epidemiological evidence to support even the most restrictive reading of *Daubert/Havner/Garza*.

III. WHAT ABOUT THE EPI?

Abbott takes the position that epidemiology is all-encompassing and scientifically determinative, arguing, essentially, that the scientific verdict is in and that Abbott wins. It is not surprising.[6] In so doing, it ignores federal procedure, state burdens of proof, and the Seventh Amendment. Abbott's arguments in this regard are wrong on the science, wrong on the law, and wrong on the facts.

A. The Practical Limitations of Epidemiology. To put Abbott's arguments in context, it is important to outline what epidemiology can and cannot do. Fortunately, the Court is not without objective guidance. The 2011 federal REFERENCE MANUAL OF SCIENTIFIC EVIDENCE, *Reference Guide on Epidemiology*, (3rd Edition, 2011) is an invaluable tool. First, we must understand that the field of epidemiology is not designed to address specific causation of any disease process in any individual patient. Rather, "epidemiology is the field of public health and medicine that studies the incidence, distribution, and etiology of disease in human *populations*. *Id*. at 335 (emphasis added). Because the focus is on a population at large, it is not surprising that it is not particularly helpful in determining specific causation:

> Epidemiology is concerned with the incidence of disease in populations and *does not address the question of the cause of an*

[6] There is evidence that Abbott itself quietly bought and paid for much of this favorable scientific literature. This is a strong statement and we do not make it lightly. In point of fact, of the 20 epidemiological studies cited by Defendant in its motion, at least seven of them are authored or coauthored by an Abbott Key Opinion Leader who is not an "Independent," but rather is held by Abbott to be either"True Partners," "Advocates," or "Supporters." *See* FN 20, 30 to Plaintiff's *Daubert* Opposition.

> *individual's disease.*. This question, sometimes referred to as specific causation, is *beyond the domain of the science of epidemiology*. . . . epidemiology addresses whether an agent can cause a disease, not whether an agent did cause a specific plaintiff's disease.

Id. at 382 (Emphasis added). For an example of a case concerning lymphoma, and discussing the practicing limitations of epidemiology, *see Knight,* 482 F.3d at 354 cited by Abbott. In reality, it stands principally as an example of the breadth of judicial discretion in deciding these kinds of motions.

Nor, indeed, does epidemiology "objectively" prove general causation. Rather, epidemiology provides a framework for a causality assessment that is always, one of *subjective* professional judgment by a qualified expert. *See e.g., Wells,* 601 F.3d 375 at 380 ("We ... understand that in epidemiology hardly any study is ever conclusive, and we do not suggest that an expert must back his or her opinion with published studies that unequivocally support his or her conclusions.").

Even with regard to the topic of general causation, there are definite limits regarding what epidemiology can or cannot show. The field originated in circumstances where there was usually one cause of a disease or harm. In those circumstances, the process of attributing risk, excluding alternative possibilities, etc., that is inherent in the science of epidemiology, can be very helpful. But when the adverse event is one that is, almost by definition multi factorial, like cancer in this case, then the problem becomes exceedingly more complex. A drug can contribute in a material way, or, as most states require, be a "substantial factor" in the development of a disease state or adverse event, even though other factors, like age, genetics, preexisting disease state, or other medications may also contribute. But in Texas as in most states, juries are regularly instructed that there may be more than one cause present to produce an injury, and more than one person legally responsible for an injury. The plaintiff does not have to prove that the defendant's breach was the only or predominant cause of the injury. If two or more causes operating together contributed to the

plaintiff's injury so that, in effect, the damages suffered were inseparable, then it is enough for the plaintiff to prove that the defendant's product was a substantial contributing factor in causing the injury.

As the *Reference Guide* states, "epidemiology cannot objectively prove causation; rather, causation is a *judgment* for epidemiologists and *others* interpreting the epidemiologic data." *Reference Guide* at 374. Moreover, "[m]ost researchers are *conservative* when it comes to assessing causal relationships, *often calling for stronger evidence* and more research before a conclusion of causation is drawn." *Id*. In the experience of the undersigned, this is particularly true of those researchers who are employed by pharmaceutical companies. They almost never use the "c" word, *i.e.,* "causality" when referring to <u>any adverse side effect</u> of their company's medication. *See e.g.,* Exhibit E at 110-111 (Deposition of Dr. John Medich)[FUS] which includes the following colloquy:

> Q. Maybe I'm just having a hard time with the word "cause." Does – Does taking Humira result in bad things happening for some patients?
>
> A. It depends on what you characterize as "bad things." Patients that are treated with Humira have adverse events.

B. Abbott's Own Epidemiology Expert's Concessions Undermine Abbott's Arguments. To evaluate the *Daubert* challenge against Plaintiff's expert, it is perhaps helpful to see what Abbott's own epidemiology expert, Dr. Howard Ory, had to say. Here are some of the concessions he made in his deposition in the *Calisi* case:

a. When the confidence interval includes 1.0, an increased risk cannot be excluded.[7]

b. The point estimate is the *most likely* value of the risk.[8]

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[7] Exhibit F at 34:15-36:9 (Deposition of Dr. Howard Ory).

[8] *Id.*

c. The point estimate is the *most likely* value for the relative risk.[9]

d. Most of the Humira studies reviewed by Dr. Ory have a relative risk greater than one and therefore, an increased risk cannot be excluded and the most likely value for the true relative risk is the point estimate.[10]

e. A relative risk of 2.0 is not required to establish a causal relationship in a scientific sense.[11]

f. Dr. Ory has no opinion on the biological basis for TNF drugs contributing to the development of lymphoma.[12]

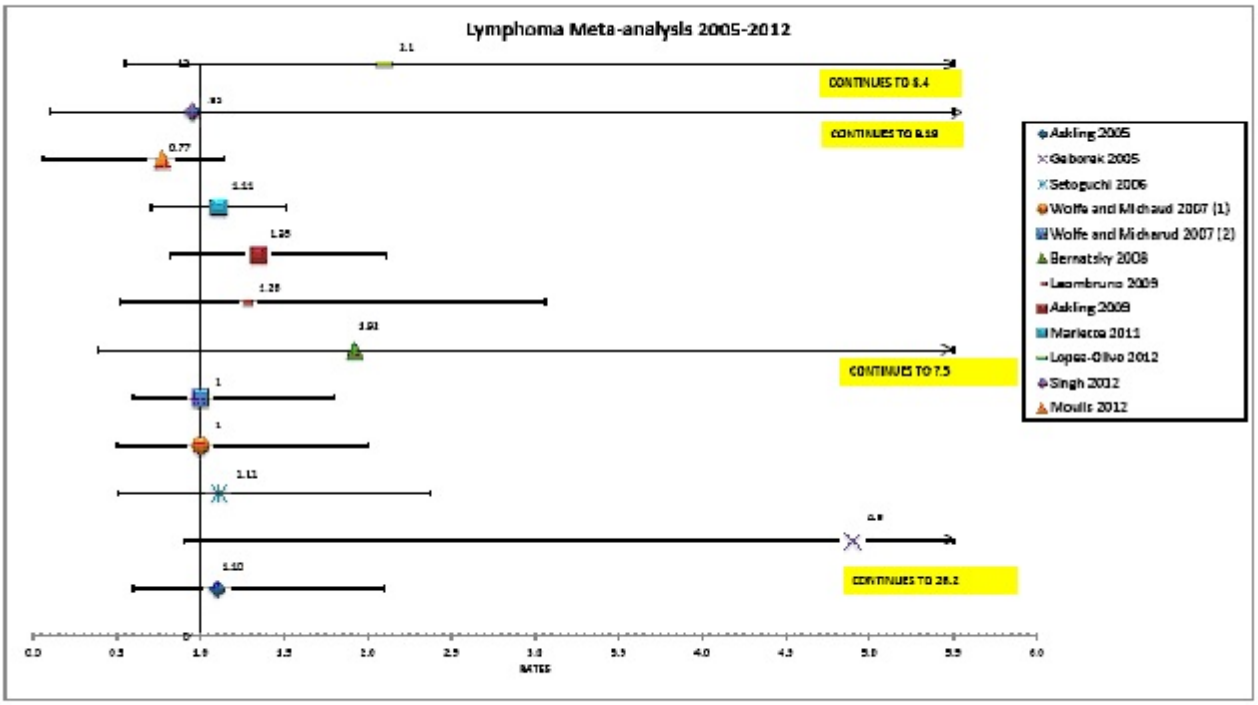
C. The Clear Epidemiological Trend Demonstrates a Positive Risk of Cancer with Humira. If a "picture is worth a thousand words," then the following table, showing the relative risks or incidence ratios between Humira or other TNF alpha blockers and lymphoma or other malignancies says it all. Also attached in full-size copy as Exhibit G for the Court's convenience. Everything to the right of 1.0, *i.e.,* the vertical line, shows a positive risk assessment. And the farther the confidence interval takes the line to the right, the greater the risk:

[9] *Id.*

[10] *Id.* at 143:13-146:8, 148:1-148:23.

[11] *Id.* at 178:25-180:7.

[12] *Id.* at 228:17-229:4.



Additionally, one of the things that is important to do with epidemiological evidence is to observe the *trends*. If there is a consistent trend showing a positive risk, then scientists take heed. The above graph depicts the 13 epidemiological articles cited by Abbott at the time of its *Daubert* briefing in *Calisi*. The trend is clear. The risk is positive. And the magnitude of that risk, given the wide confidence intervals, could be staggering.

One of the earliest and most significant papers in this context is the 2006 Bongartz paper that was published in the prestigious Journal of the American Medical Ass'n. Exhibit H (Bongartz et al. (2006) *Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infection and malignancies: Systemic review and meta-analysis of rare harmful effects in randomized clinical trials*. Journal of the American Medical Association 295: 2275-2285 (2006)). This peer reviewed publication was a meta-analysis of multiple clinical trials of anti-TNF therapy–including Humira–among RA patients. It examined risk of malignancies among the treatment versus placebo arms of

a large subset of anti-TNF therapy clinical trials. *Id.* at 2275. The authors found the pooled OR for all malignancies was a statistically significant 3.3 (95% CI,1.2-9.1). *Id.* Malignancies were significantly more frequent in patients treated with higher doses (OR = 4.3) compared with patients compared with patients who received lower doses (OR = 1.4) of anti-TNF drugs. *Id.* These result were statistically significant.[13]

A positive dose-response relationship, as seen in Bongartz, is a classic hallmark of a drug induced effect. It is recognized as such by Bradford-Hill, *The Reference Manual on Scientific Evidence,* as well as the FDA in its Guidance for Industry on warnings. Exhibit A at 3.[14]

Abbott ignores this article, hoping that it will be perceived as an outdated and unimportant piece of inconvenient epidemiological data. Unfortunately for Abbott, the FDA does not. Exhibit L hereto is a September 2012 letter from the FDA to Abbott Laboratories approving Humira for ulcerative colitis. On pages two and three the FDA writes:

> "In addition, there are literature reports of an increased risk of serious adverse events in patients receiving higher doses of Humira (adalimumab), including opportunistic infections and **malignancies**. We consider this information to be '**new safety information**' as defined in section 505-1(b)(3) of the FDCA.

Id. at 2-3. As support for this statement, the FDA cites in FN 1: "Bongartz T, et.al. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies:

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[13] The publication of this article caused quite the stir within Abbott. In response to the Bongartz publication, Abbott specifically orchestrated an "action plan" to discredit, minimize, and criticize the study results. Exhibit I at 1 (JAMA Response Strategy)[FUS]; Exhibit J (May 2006 Email Bongartz Publication)[FUS]. Included in their plan was soliciting advise, strategy, and the assistance of their "non-independent" Key Opinion Leaders, Schiff, Cush, and Kavanaugh. Exhibit J. Components included a communications strategy, publication, and sales force talking points. *Id.* It should not surprise the Court that these individuals are the lead authors of many of the "studies" cited by Abbott in its motions.

[14] Interestingly enough, and not mentioned by Abbott is that when one of its KOL's was asked to review the Bongartz study, that found both a statistically significant increased risk of malignancies in persons taking TNF-blockers and a dose response relationship, he stated that "the methodology was OK," that "this is a true safety signal...that should be taken seriously....", and that he does " believe the dose story." Exhibit K to Plaintiff's SUMFs at 2 (Klareskog email)[FUS].

systematic review and meta-analysis of rare harmful effects in randomized controlled trials. JAMA 2006 May 17;295(19):2275-85. Id. at 3."

Other epidemiological evidence also points to a positive risk. Here are several that were discussed in the report of Dr. David Goldsmith that Dr. Gershwin reviewed and relied upon in addition to Bongartz:[15]

> Mariette et al., *Lymphoma in Patients with Anti-TNF: Results of the Three Year Prospective French RATIO Registry*, 69 Ann. Rheum. Dis. 400, 404 (2010) (**Finding statistically significant odds ration of lymphoma after last using Humira or Remicade of 6.68 (1.90 to 23.54, p=.003**); authors state that "[s]ome lymphomas associated with immunosuppression may occur and the risk of lymphoma is higher with monoclonal antibody therapy [Humira] than with soluble receptor therapy." Exhibit M at 400, 404.
>
> Geborek found a RR for lymphoma of 4.9 (95% CI .9 to 26.2). Exhibit N at 699 (Geborek P et al., *Tumour necrosis factor blockers do not increase overall tumour risk in patients with rheumatoid arthritis, but may be associated with an increased risk of lymphomas*. Ann Rheum Dis. 2005 May;64(5):699-703.). **This study also documented a statistically significant relative risk of 11.5 (95% CI 3.7 to 26.9) in anti-TNF treated patients for the development of lymphoma. *Id*. at 699, 702.**
>
> Leombruno found an OR for lymphoma of 1.26 (95% CI .52 to 3.06). Exhibit O to at 1136 (Leombruno JP et al., *The safety of anti-tumour necrosis factor treatments in rheumatoid arthritis: meta and exposure-adjusted pooled analyses of serious adverse events*. Ann Rheum Dis. 2009 Jul;68(7):1136-45.)
>
> Wolfe found a **statistically significant** increased risk of lymphoma when comparing persons with RA taking Humira and methotrexate verse all other treatments (**OR=5.6 CI 95% 1.1 to 29.0**), and a borderline statistically significant increased risk of lymphoma for those taking Humira verse all other medications (OR=4.5 CI 95% .9 to 23.1. Exhibit P at 1437 (Wolfe F et al., *The effect of methotrexate and anti-tumor necrosis factor therapy on the risk of lymphoma in*

[15] Abbott's conjecture about why plaintiff chose to limit the number of experts in this case is purely that, *i.e.,* conjecture. Because Dr. Goldsmith has been withdrawn, there is no need to address the specifics of his report or his potential testimony. However, the evidence that he marshaled, some of which is chronicled here, was considered by both Dr. Gershwin and Dr. McCracken and does support their causation opinions in this case.

> *rheumatoid arthritis in 19,562 patients during 89,710 person-years of observation*. Arthritis Rheum. 2007 May;56(5):1433-9.)
>
> Bernatsky found an adjusted RR of 1.92 (95% CI .49-7.5) for hematological cancers. Exhibit Q at 280 (Bernatsky S et al., *Hematologic malignant neoplasms after drug exposure in rheumatoid arthritis*. Arch Intern Med. 2008 Feb 25;168(4):378-81.)
>
> Askling found a RR for lymphoma of 1.35 (95% CI .82 to 2.11). Exhibit R at 648 (Askling J et al., *Anti-tumour necrosis factor therapy in rheumatoid arthritis and risk of malignant lymphomas: relative risks and time trends in the Swedish Biologics Register.* Ann Rheum Dis. 2009 May;68(5):648-53.)
>
> Askling found a hazard ratio of 2.69 (95% CI .91 to 8.21) for all site cancer excluding non-melanoma skin cancer when looking at Outcome C. Exhibit S at 125 (Askling J et al., *Cancer risk with tumor necrosis factor alpha (TNF) inhibitors: meta-analysis of randomized controlled trials of adalimumab, etanercept, and infliximab using patient level data*. Pharmacoepidemiol Drug Saf. 2011 Feb;20(2):119-30.)

As Defendant's epidemiologist has stated "a point estimate is the most likely estimate of relative risk comparing the risk of, say, a substance and an outcome, like a disease, and the confidence interval." Exhibit F at 25:18-25:23. And the above point estimates all point to a most likely estimate that Humira increases the risk of lymphoma.[16]

Another publication worth examination as an exemplar of the rampant conflicts in Abbott's cited literature is that of Cush *et al.*, *Does Rheumatoid Arthritis or Biologic Therapy Increase Cancer Risk?*, 4(2) Drug Safety Quarterly 1 (2012). Exhibit U. Both the main author of this piece, Dr. Jack Cush, and the organization it was published under–the American College of Rheumatology

[16] As stated earlier, a recent meta-analysis is a September 2012 JAMA article evidencing a point estimate of 2.1 (95% CI, .55-8.4) for lymphoma for TNF-blockers. Exhibit T (Lopez-Olivo MA et al., *Risk of Malignancies in Patients With Rheumatoid Arthritis Treated With Biologic Therapy: A Meta-analysis*. JAMA. 2012;308(9):898-908.) at 898. This article was published in JAMA in September 2012 and includes data from 63 randomized , placebo control trials with a total study population of 29,423 patients. *Id.* The authors note that "[m]ost observational studies have found increased risk of malignancies ranging across studies, with relative risks (RRs) of 0.7 to 2.7 for all types of malignancies, 1.1 to 5.0 for lymphoma....". *Id.* at 899. Lastly, the authors state that the "risk of lymphoma with TNF inhibitors was doubled but did not reach statistical significance." *Id.* at 901.

(ACR)–have conflicts of interest when it comes to TNF-blockers. First, Dr, Cush is Key Opinion Leader ("KOL") for Abbott. Exhibit V (Humira Psoriasis Approval Plan)[FUS].[17] Dr. Cush is not an "Independent" KOL, rather, according to Abbott's own internal rating scheme, he is a Humira "Advocate." *Id*. at 13. He has received more than $10,000 from Abbott for consulting fees, speaking fees, and/or honoraria. Exhibit W at 1 (Cush Conflicts). Dr. Cush does not mention these conflicts of interest in this article. Additionally, Abbott donates tens of millions of dollars to ACR. Exhibit X at 66 (PsA Structural Damage & Physical Function Indication Teleweb)[FUS]. This conflict is likewise not mentioned in this article. The citation of this Abbott authored, ghost-written paper is really an example of the pot calling the kettle black! Further misleading the Court, the Cush paper is not from a peer-reviewed publication and is written by the co-editor of the American College of Rheumatology's Drug Safety Quarterly. All three authors cite to extensive drug company involvement calling into question the appropriateness of even considering such a paper. It is nonsensical for Abbott to claim that these authors (or the organization for that matter) constitute an independent scientific body.

The Solomon paper identified by Abbott[18] shows that the majority of the papers considered have point estimates above one for lymphoma. Interestingly, this paper also stated the following:

> Most studies demonstrated a numerically increased risk for lymphoproliferative cancers (18,19,22,23) and nonmelanoma skin cancers (NMSCs) (21,24). Increased risk estimates for lymphoma ranged from 1.1 (95% confidence interval [95% CI] 0.6–2.1) (19) to 4.9 (95% CI 0.9–26.2) (22), with 4.9 being an outlier and more values falling near the estimate of 1.1. However, 2 studies indicated no additional risk of lymphoma among patients receiving TNF inhibitors (24,25).

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[17] "FUS" will designate that this exhibit or record reference has been marked as confidential by Abbott. As such, it will be filed under seal.

[18] Abbott's *Daubert* Motion at 28.

Id. at 29.[19]

IV. THERE ARE AT LEAST TWO EPI STUDIES WITH RELATIVE RISKS OF 2.0+.

Finally, it should be noted here, as in our response to Abbott's *Daubert* motion, that there **are** more than two epidemiological studies that identify a statistically significant relative risk in excess of 2.0. One is the 2006 Bongartz article in JAMA, that Abbott tried so hard to discredit. The authors found the pooled OR for all malignancies was a statistically significant 3.3 (95% CI,1.2-9.1) for patients taking TNF-inhibitors including Humira. Exhibit H. The other is the Wolfe study, Exhibit P. It found a statistically significant risk of lymphoma when comparing persons with RA who were taking Humira and methotrexate to all other treatments. (OR = 5.6, CI 95% 1.1 to 29.0). Yet another is the Mariette et al., *supra* Exhibit M, that found a statistically significant odds ration of lymphoma after last using Humira or Remicade of 6.68 (1.90 to 23.54, p=.003) as well as the Geborek study, *supra*, Exhibit N, a statistically significant relative risk of 11.5 (95% CI 3.7 to 26.9) in anti-TNF treated patients for the development of lymphoma..

Even more fundamentally, Abbot admits that its own internal clinical trial data showed a statistically significant increased rate for lymphoma in RA patients taking Humira prior to the drug ever going on the market. Here is what their Vice-President and clinical trial 30(b)(6) witness, Dr. John Medich, stated under oath:

> Q. And this, so we understand what it is, this is Abbott's summary of all the safety data in the clinical trials that were being provided to the FDA when you asked for permission to sell this drug?
>
> A. That is correct.

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[19] The authors of the Singh paper Abbott cites on page 12 of its motion specifically describe their results in the following manner: "Over the short time frame of these trials there may be little or no difference in the number of people who experienced cancer while taking any biologic compared with people who took placebo. However there were not many cases of cancer so our confidence in this result is low." *Id*. at 3. *See* Exhibit D at ¶¶ 106-110 to Plaintiff's *Daubert* motion for discussion of each of the scientific articles that Abbott highlights on page 11-12 and the limitations and conflicts of interest for them.

Q. And over, if you would, on page 00160671.

A. Okay. I'm there.

Q. What is the title of this paragraph 6.2.6?

A. "Malignancies."

Q. And you want to read the first sentence, or you want me to do it?

A. I can read the first sentence.

Q. Okay.

A. "21 patients 19 (1.4) percent of 1388 adalimumab treated patients and 2 (0.3) percent of 690 placebo treated patients were discovered to have malignancies."

Q. And the next sentence says: "Shown in Table 31, this difference was statistically significant." Correct?

A. That is what it says.

Q. So the -- Roughly speaking, you're talking about a rate of malignancies on people getting Humira is four and a half times higher than patients from the same patient population who were getting placebo?

A. We're talking about a percentage difference.

Q. 0.3 for placebo, and 1.4 percent for Humira right?

A. Yes.

Q. Which is roughly four times higher, right?

A. As a percentage basis, yes.

Q. And this is statistically significant data?

A. It is statistically significant with a P value of less than .05.

Exhibit Y at 72:22-74 [FUS].

Abbott equally admitted that there was a statistically significant increased risk of lymphoma found in Humira clinical trials before Humira went on the market:

> Q: The expected rate of malignancies in RA trials is 2.3, but the SIR is 4.8, right?
>
> A. We're looking at all lymphomas?
>
> Q. All lymphomas, right.
>
> A. So expected based on the SEER database is 2.3.
>
> Q. And we know from the confidence interval to the right, from 2.4 to 8.6, that it's statistically significant?
>
> A. Yes.

Id. at 90:13-91:2 [FUS].

Finally, a word should be said about Dr. Gershwin's candid acknowledgment that, for some patients, Humira's anti-inflammatory effects might actually reduce the risk of cancer. Two things. First, this does not mean that it does not, through immunosuppression, increase the risk in other patients, like Gayathri Murthy. Second, IF Humira reduces the risk for anyone, then, logically, the relative risk should be below 1.0, not above it. And, yet, the consistent positive risk data in all of the published epidemiological studies stands out as very strong corroborative proof that the Humira label is right. Humira can in fact cause cancer.

V. PLAINTIFF'S EXPERT OPINIONS ARE CORROBORATED BY ABBOTT'S SUBSEQUENTLY PRODUCED ADVERSE EVENT DATA WITH CAUSALITY ASSESSMENTS.

Dr. Gershwin's report in this case was dated June 18, 2012. Because all of the document production has been done across the entire spectrum of Humira litigation, Abbott has continually and sporadically produced relevant documents. A number of them were produced by Abbott to Plaintiff on January 16, 2013 and received by Plaintiff on January 17, 2013. *See* Exhibit Z. These documents, along with roughly 15,000 pages of adverse event reports, were provided to Plaintiff's

counsel the day before the 30(b)(6) deposition of Dr. James Embrescia, Abbott's designee for pharmacovigilance/adverse event reports for all malignancies, including lymphoma. There are four key documents that contain admissions that corroborate Dr. Gershwin and Dr. McCracken's causation opinions. The four documents include:

1. Exhibit Z1-ABT_07241850-ABT_07241851- Suspect adverse reaction report of non-Hodgkin's lymphoma in a rheumatoid arthritis patient wherein Abbott's causality assessment found that the lymphoma was *probably related* to Humira.

2. Exhibit Z2-ABT_07242696-ABT_07242694- Suspect adverse reaction report of Hodgkin's lymphoma wherein Abbott's causality assessment found that the lymphoma was *probably related* to Humira.

3. Exhibit Z3- ABT_07245818-ABT_07245821- Suspect adverse reaction report of cervix carcinoma wherein Abbott's causality assessment found that the malignancy was *probably related* to Humira. The reporter of the information determined that the relationship was "possible" and Abbott determined "probable."

4. Exhibit Z4- ABT_07253647-ABT_07253649- Suspect adverse reaction report of breast cancer wherein Abbott's causality assessment found that the malignancy was *probably related* to Humira. The reporter of the information determined that the relationship was "possible" and Abbott determined "probable."

These are, of course, not the only pertinent, unpublished, internal, damning documents. For example, a series of email documents, attached hereto as Exhibit AA [FUS], establish that, in 2008, a case of cancer was diagnosed by Abbott Key Opinion Leader Dr. Jack Satsangi in Scotland. The diagnosis of Humira induced cancer, with positive dechallenge evidence, was confirmed, and, behind closed doors, admitted in private by Abbott scientists: "...the case does clearly demonstrate a link between adalimumab and this tumour." *Id.* at 1.

Abbott exerts great energy trumpeting the benefits of Humira. There is little doubt that Humira has helped many people with their RA. And Abbott has reaped the financial windfall that has come along with that. However, there is no exception in the law for beneficial products when

it comes to the duty to clearly and unambiguously warn about risks. Regardless of Humira's purported efficacy, Abbott still has the responsibility to be forthright about the dangers of Humira. The evidence before the Court, including Abbott's internal acknowledgment of definitive risk and the statistically significant internal clinical trial data, all corroborate the causation opinions that Humira, can, indeed, cause cancer, and did so with respect to Mrs. Murthy. The statistically significant data that is available equally support this conclusion.

Conclusion

This federal case should be decided on federal evidentiary and procedural standards. Because there is sufficient evidence regarding both general and specific causation, Abbott's motion should be denied, and the case should proceed to trial as scheduled on October 7, 2013.

Respectfully submitted,

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Certificate of Service

I certify that on this 30th day of July, 2013, Plaintiff's Response in Opposition to Defendant's Motion for Summary Judgment on Causation has been electronically filed with the Clerk using the CM/ECF system, which will automatically send email notifications of such filing to the following attorneys of record:

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